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STUDIES IN INFLUENZA AND PNEUMONIA

XI. THERAPEUTIC EFFECTS OF A MONOVALENT ANTISTREPTOCOCCUS SERUM IN INFLUENZA AND INFLUENZAL PNEUMONIA

E. C. ROSENOW

Division of Experimental Bacteriology, The Mayo Foundation, Rochester, Minnesota.

In this study I shall record the results obtained in the treatment of influenza and influenzal pneumonia with the serum prepared with one strain of the green-producing streptococcus, and a study of the immunologic condition of the streptococcal flora of the sputum made at the same time in the patients receiving the serum injections.

The serum was used in undoubted and, with one exception, in severe cases only. All injections were made slowly intravenously. The amount injected at one time varied from 25 cc to 100 cc of the undiluted serum. In some instances a desensitizing dose of 1 cc was given one hour previously. Twelve patients were given the serum. These may be conveniently divided into three groups according to the agglutination tests and therapeutic results.

Group 1 (Four Patients).—The sputum of all contained predominating numbers of green-producing streptococci which were agglutinated specifically by the monovalent serum. All four patients showed marked improvement and recovered promptly following the serum treatment. Three of the patients were experiencing the initial influenzal attack, and one had a recrudescence at the time of the serum treatment. The lung findings remained limited; none of the patients developed outspoken signs of extensive consolidation. In at least two, the improvement seems definitely attributable to the serum since the lung findings and symptoms were on the increase at the time of the serum treatment (cases 1, 2 and 3, and chart 1).

Case 1 (3283).—Mrs. H. C. L. came to the Clinic March 11, 1919, on account of nervousness, general weakness, fluttering of the heart and profuse menstruation. The symptoms followed a severe attack of influenza in October, 1918. Examination revealed a pelvic tumor for which a hysterectomy was advised.

March 28 the patient was admitted to the isolation hospital, with symptoms of influenza. She had been taken ill five days before with moderate headache, aching in the arms and back, sore throat, cough and slight nausea. These symptoms grew gradually less severe until the day before admission to the hos-

pital, when she became worse with general aching, chilly sensations in the back, but no distinct chill or fever. The patient's throat was diffusely red, her tongue coated, she was cyanotic, and crackling râles were elicited over the bases of both lungs, especially on the right side. Findings of the heart, blood and urine were normal. On the day of admission the sputum was slightly blood streaked. No evidence of consolidation was noted at any time. A culture of the sputum showed predominating numbers of green-producing streptococci and a few staphylococci, and the primary culture in dextrose-blood broth was agglutinated specifically by the serum from horse 15 (table 1). March 29 the patient was given 50 c c of this serum; the aching disappeared during the course of the day, the cough lessened, and the following day the temperature dropped perceptibly and became normal (chart 1). The leukocyte count was 7,300 the day after admission and rose to 13,500 March 31 and April 1. The patient made an uneventful recovery.

Case 2 (3208).—A farmer of middle age, entered the hospital March 11, 1919. He complained of severe backache, headache, inability to sleep, sore throat and cough. The illness had begun the previous day with chilly

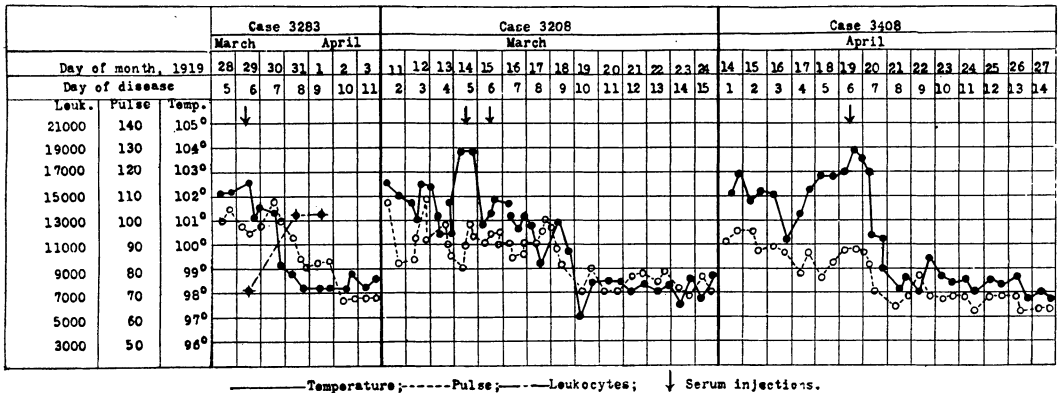


Chart 1.—Temperature, pulse and leukocyte curves in three patients in whom specific agglutination of the green-producing streptococcus from the sputum was obtained, and in whom marked improvement followed injection of the monovalent serum. In this and the following charts temperature is indicated by a solid line; leukocytes by a long dash line; pulse by a short dash line, and serum injections by arrows.

sensations but there had been no distinct chill. The patient's lips and finger-nails were moderately cyanotic, he was mentally apathetic, although he complained of inability to sleep. His throat was diffusely red. The tonsils were also congested and the tongue was heavily coated. In the night of March 13 severe hemorrhage from the nose occurred and continued at intervals the following day. The lung findings were negative until March 17 when a small area of dulness was found at the inferior angle of the left scapula with slightly increased vocal fremitus and a suggestion of bronchial breathing. Later in the day dulness at the left base of the lung, fine crepitant râles in showers, and distinct bronchial breathing, especially at the inferior angle of the scapula near the spine, were noted. The sputum at first was mucopurulent, but March 13 it became serous in character and streaked with blood. Leukopenia was marked (chart 1). Blood-agar-plate cultures of the sputum obtained March 13, 15, and 17, showed countless numbers of green-producing streptococci, a

TABLE 1

AGGLUTINATION EXPERIMENTS WITH CULTURES FROM THE SPUTUM IN CASES OF INFLUENZA
AND INFLUENZAL PNEUMONIA IN WHICH IMMUNE SERUM WAS USED

Case	Date on Which Sputum Culture Was Made	Condition of Culture at Time of Agglutination Test Dextrose-Blood-Broth Inoculated with	Antiserums					Controls	
			Pneumococcus			Streptococcus		Normal Horse Serum	NaCl Solution
			I	II	III	Hemo- lytic of Horse 9	Green- produc- ing of Horse 15		
3208	3/13/19	Single green colony streptococcus.....	0	0	0	0	+++	0	0
		Green-producing streptococcus after one animal passage.....	0	0	0	++	++++	0	0
		Green-producing streptococcus in third generation after one animal passage...	+	+	+	+	+++	0	0
3276	3/28/19	Washed sputum.....	0	0	0	0	+++	0	0
		Blood of mouse dead from intraperitoneal injection of sputum. Pure green streptococcus.....	++	++	++	++	++++	++	0
		Washed sputum.....	0	+	+++	+	++	+	0
		Blood of guinea-pigs injected intratracheally with moist, spreading greenish colony of streptococcus from sputum.....	0	0	+++	0	0	0	0
3282	4/ 2/19	Washed sputum.....	0	0	++	++	0	0	0
3282	3/30/19	Washed sputum.....	0	+++	+++	+++	++++	0	0
		Washed sputum.....	0	++	+	++	+++	0	0
3283	3/30/19	Washed sputum.....	0	0	0	0	+	0	0
		Single colony moist, green streptococcus.....	0	+	0	+	++	0	0
3338	4/ 7/19	Washed sputum.....	0	0	0	++	++++	+	0
	4/ 8/19	Swab from throat.....	0	0	0	0	+	0	0
	4/ 9/19	Washed sputum.....	0	0	0	+	++	0	0
	4/11/19	Washed sputum.....	0	++	0	++	0	0	0
	4/13/19	Washed sputum.....	+	+	+	+	+	+	+
		Single colony green-producing streptococcus from sputum.....	+	0	+	++	++	+	0
	4/16/19	Washed sputum.....	0	0	0	0	0	0	0
	4/17/19	Washed sputum.....	0	0	0	++	++	0	0
	4/25/19	Exudate right lung (hemolytic streptococci).....	0	++	0	+++	0	++	0
		Exudate right lung (hemolytic streptococci).....	+	+	+	+++	+	+	0
3341	4/ 8/19	Tonsil swab.....	0	0	0	0	0	0	0
	4/ 9/19	Washed sputum.....	0	+++	0	0	++	0	0
	4/11/19	Washed sputum.....	0	+++	++	++	++	0	0
	4/12/19	Single colony green streptococcus.....	0	+++	0	+++	++	0	0
3402	4/17/19	Throat swab.....	0	0	0	0	0	0	0
		Washed sputum.....	+	+	+	+	+	+	+
3408	4/18/19	Washed sputum.....	0	0	0	0	++	0	0

few staphylococci, but no hemolytic streptococci nor influenza bacilli. A blood culture made March 12 was negative. Dextrose-blood-broth cultures of the green-producing streptococcus isolated directly from the sputum March 13 and from the lung of a guinea-pig injected intratracheally with the sputum were agglutinated specifically by the serum of horse 15 (table 1). March 14 the patient's condition was very serious. Cyanosis was increasing, the sputum became more bloody and frothy, the mental apathy was worse, and prostration and epistaxis were marked. In the afternoon the patient was given 60 c c of the serum intravenously. The hemorrhage from the nose stopped, the patient's general condition became much better, and he was brighter mentally soon after the injection. The following day the injection of serum was repeated. The temperature dropped gradually to normal, and uneventful recovery followed (chart 1). The effect of the serum in this case appeared strikingly favorable, and probably was not coincident, since the symptoms and lung findings were on the increase at the time the serum was given. A slight urticarial rash developed ten days later. This patient was one of a group of five from the same locality who had severe attacks of influenza within a few days of each other after their arrival in Rochester; two of the patients died.

Case 3 (3408).—A middle aged man, entered the hospital April 14, 1919. He complained of severe aching, headache, malaise, weakness, sore throat, and slight cough. A general examination revealed moderate cyanosis, without manifest dyspnea, mental apathy, a diffusely red throat, and coated tongue. The chest findings were negative on the day of admission, but bubbling râles over both chests were elicited posteriorly April 15, 16, 17 and 18. The sputum obtained April 18 was mucopurulent. The cultures showed countless numbers of staphylococci and a moderate number of rather moist, spreading, green-producing and hemolytic streptococci. The leukocyte count on the fifteenth was 4,700. A blood culture made on the nineteenth proved negative. The primary culture of the washed sputum in dextrose-blood broth was agglutinated specifically by the serum of horse 15 (table 1). April 19, 25 c c of the serum were injected intravenously; the temperature and pulse rate dropped rapidly, and the general improvement was marked. The patient recovered promptly.

Group 2.—The three patients in this group were treated with the serum, and all showed marked improvement following injections during the initial attack of influenza when the green-producing streptococci from the sputum were agglutinated specifically by the monovalent serum. Later the patients developed bronchopneumonia due to green-producing streptococci that were not specifically agglutinated by this serum or by any of the immune serums tested (table 1, cases 4 and 5, and chart 2).

Case 4 (3282).—A woman, aged 48, came to the Clinic because of the recurrence of an abdominal tumor which had been operated on two years before. She was admitted to the isolation hospital March 28, 1919, stating that she had become ill the day before with a severe chill, sore throat, headache, and severe general aching. Her lips and fingernails were cyanotic, she was short of breath, even when lying quietly in bed, and abundant crepitant râles were found posteriorly at the left base of the lung and on the right side. A culture of the sputum obtained on the day of admission showed a

large number of staphylococci and green-producing streptococci, and duplicate cultures in dextrose-blood broth were agglutinated specifically by the serum of horse 15 (table 1). March 29 and 30, 80 c.c. and 60 c.c., respectively, of the serum of horse 15 were given intravenously. The patient's general condition improved following both injections, and her temperature and pulse rate dropped to normal (chart 2). The temperature remained normal for four days, and the abnormal lung findings almost disappeared. On the fifth day the temperature again rose and remained high for nine days, the pulse was rapid, and a sharp rise in the leukocyte count occurred. On the day following the rise of temperature an urticarial rash covered the entire body. With the increase in the temperature, dulness, bronchovesicular breathing and crepitant râles developed over the right side below the angle of the scapula. A culture of the sputum on the first day of normal temperature which followed the injection of the serum showed countless numbers of green-producing streptococci and staphylococci. The primary culture in dextrose-blood broth was

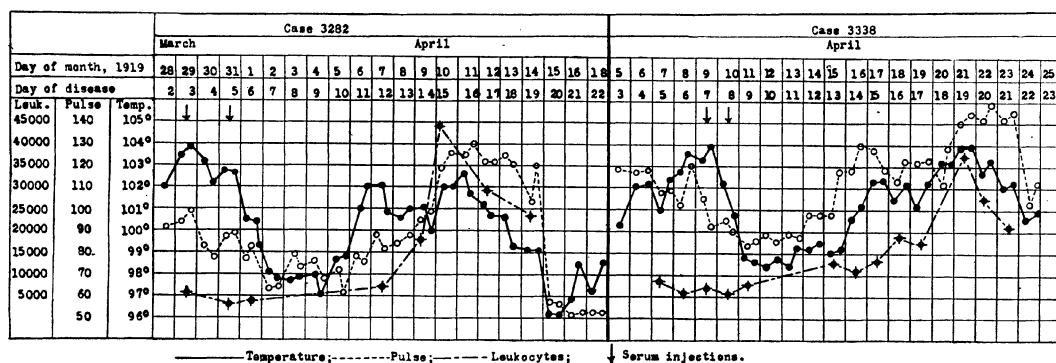


Chart 2.—Temperature, pulse and leukocyte curves in two patients in whom specific agglutination of the streptococcus was obtained during the initial attack, in whom there was marked improvement following injection of the monovalent serum, and in whom immunologically different green-producing streptococci were found during a reinfection.

again agglutinated specifically by the serum of horse 15. No cultures of the sputum were made subsequently. During the latter part of the attack of pneumonia, as the pulse rate crossed the temperature line (chart 2), the patient's condition was extremely critical for a number of days, but she finally made a complete, although slow, recovery.

Case 5 (3338).—A woman, aged 39, housekeeper, entered the isolation hospital April 5, 1919. Three days before the patient had felt chilly and could not get warm; she complained of moderate aching and was stiff in the joints and muscles. Two days afterward she developed a cough with a slight sore throat, and a moderately severe headache. If quiet in bed, she appeared well, but her lips and fingernails were decidedly blue. The examination of the chest was negative. On the morning of April 7 appeared a small area of slightly decreased resonance, bronchovesicular breathing, and a few râles below the angle of the left scapula near the posterior axillary line. The evening of April 8, crackling râles were heard on both sides in the lower axillae and posteriorly. On the morning of April 9 there were impaired resonance and

crackling râles over the left base behind and at the side, and crackling râles on the right base posteriorly. The sputum was blood tinged and serous. By evening there was dulness over both lower lobes, but no definite bronchial breathing; crackling râles were heard over the entire chest. A culture of the sputum April 7 showed countless numbers of staphylococci and green-producing streptococci, a few hemolytic streptococci, and a moderate number of influenza bacilli. The primary culture in dextrose-blood broth of the washed sputum obtained April 7 and 9, and of a throat swab, showed almost pure cultures of green-producing streptococci which were agglutinated specifically by the serum of horse 15. Accordingly the patient was given intravenously 100 c.c. of serum April 9 and 10, respectively. The patient's general condition improved following both injections, the cyanosis became less marked, the expectoration diminished, and a drop in temperature and pulse rate occurred, the temperature reaching normal the day after the second injection (chart 2). The temperature remained normal for two days and then began to rise again, as evidence of a new involvement of the lung developed. The pulse rate remained high and continued unusually high throughout the fatal recurrence. Cultures of the sputum obtained on April 11, 13, 17 and 18 showed countless numbers of staphylococci, green-producing streptococci, an increasing number of hemolytic streptococci, and a few influenza bacilli. The green-producing streptococci, however, were no longer agglutinated specifically by the serum of horse 15 (table 1). The leukocyte count was persistently low throughout the first attack of fever, and at the onset of the recurrence, but then it rose to a high point, the maximum (43,000) being reached on the sixth day. On the two subsequent days the leukocytes diminished markedly and the patient died on the following day from what appeared to be cardiac failure from an overwhelming toxemia. After death the lung showed green-producing streptococci, hemolytic streptococci, and staphylococci, but no influenza bacilli. Duplicate cultures in dextrose-blood broth of the lung exudate showed hemolytic streptococci which were agglutinated by the antihemolytic streptococcus serum from horse 9. The reinfection in this case was clearly due to streptococci which were culturally identical, but immunologically were unlike those found during the initial attack. The anatomic diagnosis made at necropsy was: "Unresolved influenzal bronchopneumonia; marked enlargement of the tracheobronchial lymph nodes; purulent hemocatarrhal tracheal bronchitis; bilateral serofibrinous pleuritis; marked engorgement of the venous trunks of the body; petechial hemorrhages in the lining of the stomach and duodenum; hemorrhagic cystitis and marked hyperplasia of the spleen."

Group 3.—This group consisted of five cases in which no improvement followed the injection of the serum. In none of these was specific agglutination obtained at the time of the serum treatment, and all the patients died. In one case (case 3276) the agglutination of the streptococcus isolated from the sputum shifted from the serum of horse 15 to type III pneumococcus serum. In another case (case 3341) agglutination occurred in type II pneumococcus and hemolytic streptococcus serums. In the third case (case 3402) the sputum showed hemolytic streptococci which were not agglutinated by any of the serums (table 1). In two cases in this group countless numbers of green-producing streptococci were found in the sputum which were

not agglutinated by any of the serums, and the patients were moribund at the time of the serum treatment. Cases 6, 7 and 8 illustrate the conditions found in this group of cases.

Case 6 (3276).—A farmer, aged 36, was admitted to the isolation hospital March 27, 1919. He had developed fever, backache, general aching, headache, dry throat, cough, and marked weakness the day before. On March 28 the throat was congested; the chest was negative except for a few scattered crackling râles. March 29 crackling râles and decreased resonance were found at the base of the left lung. The sputum was moderately bloody. On the afternoon of March 29 the patient was given 50 cc of serum from horse 15; the injection had no effect. April 1 there were definite signs of pneumonia on the left side, especially below the angle of the left scapula. The sputum was very frothy and bloody. The patient's condition grew rapidly worse, cyanosis and dyspnea increased, and he died from typical hemorrhagic pulmonary edema April 2. The leukocyte count was low at first, but it rose

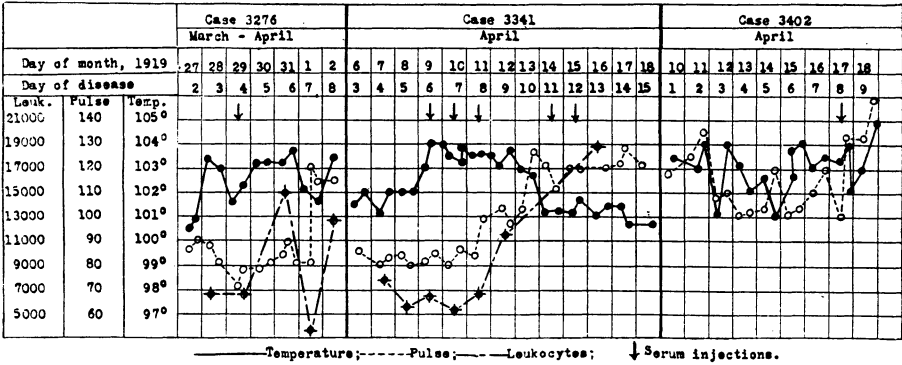


Chart 3.—Temperature, pulse and leukocyte curves in three patients in whom specific agglutination of streptococci from the sputum was not obtained and in whom the injection of the monovalent serum was without effect.

to 15,000 on March 31, and with the overwhelming toxemia showed a marked drop to 3,500 April 1, with another slight increase on the day of death (chart 3). Cultures from the sputum obtained March 28 showed countless numbers of moist, spreading, green-producing streptococci, a few staphylococci, but no hemolytic streptococci nor influenza bacilli. The primary culture in dextrose-blood broth of the washed sputum obtained on the twenty-eighth, and of the blood of a mouse, dead from intraperitoneal injection of sputum, were agglutinated specifically by the serum of horse 15. In contradistinction to this, March 30, the primary dextrose-blood-broth culture of the washed sputum, and of the moist, spreading, greenish colony of streptococci from the sputum was agglutinated specifically by type III pneumococcus serum. The primary culture of the sputum obtained April 2 was agglutinated slightly but equally by type III pneumococcus serum and antihemolytic streptococcus serum from horse 9 (table 1). The colonies on blood-agar from the dextrose-blood broth on all the days showed no change and resembled closely type III pneumococci, but they were not so elevated, and not so mucoid in character as pneumococcus mucosus.

Case 7 (3341).—A man, aged 38, undertaker, was admitted to the isolation hospital April 6, 1919. His illness had begun two nights before with a severe chill, vomiting, fever, backache, aching in the knees, general aching, slight nose bleed, and sore throat. The patient coughed and expectorated mucopurulent sputum. He was definitely short of breath and cyanotic. An examination of the chest was negative except for a few scattered râles. April 7 there were decreased resonance, and decreased breath sounds below the angle of the left scapula; April 8 decreased resonance and breath sounds and a few crackling râles were noted at the right base behind. On April 9 very definite signs of pneumonia were found on both sides. The sputum became bloody and serous. Cultures of the sputum and throat swab obtained April 7 and April 9 showed countless numbers of green-producing streptococci and staphylococci. On April 12 cultures showed countless numbers of staphylococci, a moderate number of green-producing streptococci, and larger, more moist spreading colonies resembling type III pneumococci. April 8, the primary cultures in dextrose-blood broth of the tonsil swab, and April 9, 11 and 13, of the sputum, were not agglutinated specifically by the serum of horse 15. Fermentative reactions showed that the green-producing streptococci from the sputum fermented inulin. The cultures of the sputum obtained on April 9 and 11 were agglutinated specifically by type II pneumococcus serum; those on April 13 by type II, and hemolytic streptococcus serum (table 1). The afternoons of April 9 and 10, 100 cc of serum from horse 15 were injected intravenously without effect. On April 11 and 14 injections of polyvalent anti-pneumococcus serums were given without effect. April 13 the urine showed a large amount of albumin and some red blood corpuscles. April 15 the patient was growing worse. He was bled 250 cc and was then given intravenously 250 cc of blood of a convalescent influenza patient, likewise without effect. The leukocyte count ranged from 5,500 in the earlier part of the attack to 19,200 in the latter (chart 3). The patient died April 18. The anatomic diagnosis was: "Bronchopneumonia, chronic cystitis with exacerbation, chronic parenchymatous nephritis, and old tuberculosis abscesses of the left lower lobe."

Case 8 (3402).—Woman, entered the hospital April 11, 1919; she complained of severe aching, fever, sore throat, and cough; she was toxic, cyanosed, and expectorated a small amount of mucopurulent sputum. The lung findings were negative. The heart showed mitral endocarditis with stenosis. April 14 and 15 crackling râles were elicited over both sides of the chest posteriorly, together with auricular fibrillation. April 16 the findings were definite for pneumonia of the left base. April 17 the expectorations became bloody, and profuse; the cyanosis and dyspnea increased. An injection of the serum of horse 15 had no apparent effect (chart 3), and the patient died April 18 with signs of acute hemorrhagic pulmonary edema. The sputum obtained April 17 showed countless numbers of hemolytic streptococci, staphylococci, and a few green-producing streptococci, but no influenza bacilli. The primary cultures in dextrose-blood broth of a throat swab and washed sputum were not agglutinated by any of the serums (table 1).

DISCUSSION

Of the twelve patients treated, all but one were critically ill at the time of serum treatment. Five recovered and seven died. Three of the patients who died were practically moribund at the time of the serum treatment and good effects could scarcely be expected. The

two others that died showed green-producing streptococci immunologically different from the strain with which the serum was prepared, and in two, hemolytic streptococci caused death. In these cases also improvement could not be expected. In all cases in which specific agglutination was obtained, marked improvement followed the injection of the serum, and in no case were good effects noted at a time when agglutination tests were negative.

The influenza bacilli found in the sputum in two cases might be regarded as unimportant since both patients showed marked improvement following injections of the serum. The patients treated are of course too few to permit sweeping conclusions, but since the results were controlled by immunologic studies it would seem that diplostreptococci, closely related to pneumococci on the one hand and hemolytic streptococci on the other, bear important etiologic relationship to influenza and to influenzal pneumonia, especially early in the attack. The injection of properly prepared hyperimmune serums may prove curative in cases due to organisms immunologically identical to those used in the preparation of the serum, quite as has been found in the case of type pneumococcus infections in lobar pneumonia.

The changes which occurred in bacterial flora as measured by cultural and immunologic tests during the course of the disease, emphasize the complexity of the problem and the need for their consideration in the development of specific methods of prevention and treatment of influenza and its complications.